

ORIGINAL ARTICLE

Trends in costs and prescribing for liothyronine and levothyroxine in England and Wales 2011–2020

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Abstract

Introduction: Recent prescribing policies in England and Wales have imposed significant restrictions on liothyronine prescribing in general practice driven by the prohibitive costs and uncertain benefits of liothyronine in the management of hypothyroidism. However, the impact of these policies on liothyronine usage and costs is still unclear.

Methods: Data were downloaded from the NHS monthly General Practice Prescribing Data in England and from the Comparative Analysis System for Prescribing Audit (CASP) in Wales for 2011–2020. Trends over the period in amount and costs of levothyroxine and liothyronine prescribing were analysed.

Results: The total medication costs per year for England Wales for hypothyroidism rose from £60.8 million to £129.8 million in 2015–16 and have since reduced to £88.4 million. Levothyroxine prescriptions have been growing above the population growth rate at 0.7%/annum in England and 1.1% in Wales. The costs/patient/year for liothyronine rose from £550 to £3000 in 2015–16 and has since fallen to £2500. Use of liothyronine as a percentage of levothyroxine started to fall in 2015–16 at 7%/annum in England and 3% in Wales. Nevertheless, 0.5% of levothyroxine-treated patients continue to receive liothyronine. All Clinical Commission Groups (CCGs) in England continue to have at least one liothyronine prescribing practice and 48.5% of English general practices prescribed liothyronine in 2019–20.

Conclusion: In spite of strenuous attempts to limit prescribing of liothyronine in general practice, a significant number of patients continue to receive this therapy. The price differential of liothyronine vs levothyroxine should be examined again in light of the continuing use of liothyronine.

KEYWORDS

comparison, levothyroxine, liothyronine, prescribing, T3, T4, trends

1 | INTRODUCTION

Primary hypothyroidism affects about 3% of the general population in Europe.¹ The majority of people are treated adequately with

levothyroxine (L-thyroxine). However, 5%–10% of treated hypothyroid patients report impaired quality of life, despite achieving free T4 and thyroid-stimulating hormone (TSH) levels within the laboratory reference range.² A proportion of patients with hypothyroidism,

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including those who continue to feel unwell on Levothyroxine, are prescribed liothyronine (L-tri-iodothyronine), usually in addition to levothyroxine.²

Liothyronine/levothyroxine combination therapy was originally widely prescribed when synthetic thyroid hormones first replaced animal thyroid extracts. However, with its more favourable pharmacokinetics allowing for once daily dosing, and equivocal evidence for any additional benefit of liothyronine, levothyroxine monotherapy has prevailed as the treatment of choice for primary hypothyroidism. However, early studies were small, used somewhat higher doses of liothyronine than used in clinical practice, and resulted in adverse symptoms consistent with thyrotoxicosis.³ Subsequent more recent trials failed to show convincing benefit for combined thyroid hormone replacement and thus clinical guidelines advise against the routine prescribing of liothyronine.^{4–6}

The European Thyroid Association recommends that liothyronine/levothyroxine combination therapy might be considered as an experimental approach in hypothyroidism for patients who are adherent to levothyroxine yet experience persistent symptoms despite serum TSH values within the reference range.⁴ The American Thyroid Association notes that there is currently insufficient evidence to support the routine use of combination therapy outside a formal clinical or N-of-1 trial⁵; and largely based on these guidelines, the British Thyroid Association recommends that liothyronine/levothyroxine combination therapy may only be considered by endocrinologists for patients who have unambiguously not benefited from levothyroxine.⁶

More recently in the United Kingdom (UK), the use of liothyronine has been further discouraged because of significant price inflation due to monopoly status of the generic supplier since it was debranded in 2007. The current price in 2020 of 28 tablets of 20 µg liothyronine is £165.18, compared with £26.15 in 2010 thus increasing by a factor of more than six.⁷ This has resulted in NHS England listing liothyronine as a medicine that should not be prescribed routinely in primary care,⁸ although it is still licensed. In Wales, liothyronine is categorized as a 'low priority for funding' medicine, and may not be prescribed routinely for patients who are not under the care of an endocrinologist.⁹

A small amount of natural desiccated thyroid (NDT) is prescribed by general practitioners and a few endocrinologists; because NDT has been around for so long, it did not ever need to go through the licensing process in the USA—it was classed as a 'grandfathered drug'. It has always been approved by the Food and Drug Administration (FDA) but not licensed in the same way that many other drugs have been. In the UK, it is licensed for prescription on a named patient basis. Both liothyronine and NDT are available in the UK through NHS and Private prescriptions issued by endocrinologists and general practitioners and are prescribed broadly in accordance with national guidance.⁶ Supplies of NDT prescribed in the UK come from licensed manufacturers in the USA and Canada (Armour Thyroid only).

It should be pointed out that NDT is not regulated in the same way in the UK as fully licensed preparations. Furthermore, NDT

What we knew

Increased blood testing in recent years has identified more patients with hypothyroidism and use of levothyroxine has increased. However, 5%–10% of levothyroxine users continue to experience profound and sometimes disabling symptoms, such as fatigue, depression and impaired cognition, in spite of being adherent to levothyroxine and seemingly adequately replaced from a biochemical point of view. Historically, some have been using liothyronine as an adjunct therapy, but questions over the benefits of liothyronine have resulted in existing patients being encouraged to switch back to mono therapy with levothyroxine.

What we have learnt

Levothyroxine prescribing has increased over the last years in Wales and in England, but in spite of strenuous attempts to limit prescribing of liothyronine in general practice, a significant number of doctors still prescribe liothyronine across all geographical areas.

Given how common hypothyroidism is, adequately powered clinical trials of liothyronine/levothyroxine replacement are still urgently needed.

The price ratio of liothyronine to levothyroxine is very different in the United Kingdom than in the rest of Europe and should be examined again, given that this combination continues to be prescribed widely.

which is derived from porcine thyroid gland contains both levothyroxine and liothyronine, but the balance of levothyroxine and liothyronine in NDT preparations is not the same as in humans, with a greater proportion of liothyronine which may increase risk of over-treatment and suppression of TSH.¹⁰

The aim of the study presented here was to compare the changes in liothyronine and levothyroxine prescribing in England and Wales over the period 2011–12 to 2019–20.

2 | METHODS

2.1 | Data sources

The NHS in England and Wales both publish details of prescriptions issued in primary care. In England, monthly prescribing data were obtained from NHS Business Service Authority, who publish practice-level prescribing information for all general practices including the total number of items prescribed and dispensed.⁷ In Wales, data were extracted from the Comparative Analysis System for Prescribing Audit (CASPA, CASPA.net) which contains comparable information on items and cost to the NHS, and prescribing data as in England.¹¹ The English data are publically available, while the

TABLE 1 England 2019–20 Prescribing for Hypothyroidism in Primary Care

BNF chemical	Mcg	Number of practices	Items	Actual cost	Patients annualized DDD	Act cost/ Patient year
Levothyroxine (T4) (DDD = 150 mcg)	100	7580	11,654,496	£20,523,845	798,866	£26
	50	7598	10,622,081	£19,329,359	350,343	£55
	25	7604	10,358,911	£23,189,455	174,688	£133
	75	6799	751,146	£2,254,374	34,530	£65
	12.5	3229	56,387	£162,859	441	£369
	125	143	347	£73,850	110	£673
	250	3	26	£8690	21	£414
	150	5	15	£7000	3	£2777
	200	1	3	£884	1	£896
	175	1	1	£358	0	£1867
T4 Sub- Total		7830	33,443,413	£65,550,674	1,359,002	£48
Liothyronine (T3) (DDD = 20 mcg)	20	3068	50,297	£14,603,286	6483	£2252
	5	662	3843	£1,420,942	258	£5514
	10	96	213	£72,780	15	£4967
	2.5	30	192	£82,663	7	£12,612
	25	51	178	£52,879	40	£1309
	50	3	3	£959	2	£522
Sub- Total		3238	54,726	£16,233,509	6,804	£2386
Natural Desiccated Thyroid (NDT) (DDD = 120 mg)	60	232	1358	£470,812	219	£2145
	30	141	720	£239,847	66	£3635
	120	70	251	£110,914	72	£1532
	15	48	204	£67,289	7	£9285
	90	39	145	£48,791	28	£1772
	66	18	88	£26,545	17	£1570
	65	17	59	£17,817	11	£1558
	32.5	12	48	£20,466	5	£3858
	125	5	10	£3650	3	£1383
	132	4	9	£2339	3	£918
	130	4	8	£2954	2	£1244
	33	2	6	£886	0	£1961
	100	1	5	£646	1	£1011
	180	1	1	£399	1	£694
NDT Sub-Total		382	2912	£1,013,356	436	£2327
Grand Total		7831	33,501,051	£82,797,539	1,366,242	£61

Welsh data are provided free to NHS users, general practitioners and Health Boards.¹² The database includes as above a basic price for levothyroxine and liothyronine, evaluated at national level from 2011–12 to 2019–20, a period of 9 years.

2.2 | Database analysis

For each medicine, we took the total quantity of medicine prescribed by dose and British National Formulary (BNF) code. Defined daily dose (DDD) was used to quantify medication doses.

DDD is a standard method of comparing doses of a given medication and is taken as the average maintenance dose per day of a drug administered for its main indication in adults.¹³ The amount of active agent was converted to defined daily doses by applying the levels given in the World Health Organisation and Anatomical Therapeutic Chemical (WHO/ATC) classification. For liothyronine which is most often used in combination with levothyroxine, an adjusted dose of 20 mcg/day was applied. In England, the 'Actual Cost' included adjustments for the national average discount and payments to dispensers. In Wales, the 'Basic Cost' was used.

2.3 | Data analysis

Annual trends in drug volumes, unit prices and numbers on treatment were plotted as counts or costs in British pound sterling. We calibrated prescribing of thyroid hormone replacement against the number of women in each general practice older than 25 years. In other words, the number of prescriptions as DDD was normalized for comparison between general practices by the number of women aged over 25 years old.¹⁴ The gender and age mix for each practice was taken from the population data at general practice level.¹¹ All the data used in the analyses presented are publicly available and can be made appropriately available on request from MS, co-author.

3 | RESULTS

3.1 | Current prescribing ENGLAND 2019–20

In England, 1.36 million people on the full year basis were on levothyroxine therapy and the most common tablet strengths prescribed were 100 mcg, 50 mcg and 25 mcg tablets (Table 1). Approximately

0.5% ($n = 6804$) of hypothyroid individuals were on T3, nearly all in combination with levothyroxine, and mostly at a dose of 20 mcg/day. Only 436 people were recorded as prescribed natural desiccated thyroid (NDT). The average cost of liothyronine per patient year was £2386 which was equivalent to 50 times the cost of levothyroxine at £48 per patient year.

3.2 | Current prescribing WALES 2019–20

In Wales, 88,000 people on a full year basis were on levothyroxine therapy with 3 tablet strengths most commonly prescribed (100 mcg/50 mcg/25 mcg tablets). 315 individuals equivalent to about 0.45% of hypothyroid individuals were on liothyronine, mostly in combination with levothyroxine and mostly at 20 mcg/day, similar to England (Table 2). 36 people were recorded as prescribed NDT. The average cost of liothyronine per patient year was £2729 which was approximately 57 times the cost of levothyroxine per patient per year at £53. Thus, the ratio of liothyronine to levothyroxine cost was marginally higher than in England.

TABLE 2 Wales 2019–20 prescribing for hypothyroidism in primary care

Type	Amount mcg	Number Practices	Items	Basic Price	Patients (Annual DDD)	Price/Patient/year
Levothyroxine (DDD = 150 mcg)	100	439	896,013	£1,496,216	52,541	£28
	50	434	810,819	£1,433,113	22,508	£64
	25	435	783,651	£1,573,303	10,976	£143
	75	391	49,636	£134,362	1932	£70
	12.5	189	5033	£13,853	36	£387
	125	9	21	£4000	6	£626
	250	1	3	£1398	2	£680
T4 Total		443	2,545,176	£4,656,246	88,001	£53
Liothyronine (DDD = 20 mcg)	20	168	2364	£691,184	285	£2426
	5	41	408	£152,581	25	£6048
	25	4	20	£5086	3	£1954
	2.5	2	16	£5454	0	£11,849
	10	1	10	£5313	1	£4618
	50	1	1	£545	1	£663
T3 Total		190	2819	£860,163	315	£2729
Natural Desiccated Thyroid (NDT) (DDD = 120 mg)	60	28	144	£66,659	27	£2463
	30	10	79	£24,021	6	£4354
	15	3	28	£3261	0	£8442
	125	2	7	£1805	2	£798
	120	1	3	£759	1	£923
	32.5	2	3	£122	0	£891
	65	1	1	£12	0	£1004
NDT Total		31	265	£96,639	36	£2669
Grand Total		444	2,548,260	£5,613,047	88,353	£64

3.3 | Trends over time in prescribing and cost

In England (Figure 1A), the number of individuals on levothyroxine therapy rose from 1.15 million to 1.36 million and is still growing at a rate of 3.4% per year (Figure 1A). The annual spend on hypothyroidism peaked in 2016–17 at £122 million per year of which 25% was spent on liothyronine (£30 million). The current spend is now around £83 million with 21% spent on liothyronine (£16 million).

In Wales (Figure 1B), the numbers of individuals on levothyroxine rose from 79,000 to 88,000 and is growing at a rate of 1.4% per year. Annual spend has fallen from a peak in 2015–16 of £8 million per year of which 12% was the cost of liothyronine prescriptions (Figure 1B). The current total basic price is £5.6 million with 15.4% liothyronine (£860,000). Overall, the trends were similar to England.

3.4 | Changes in levels of use and unit costs across time England and Wales

There has been a growth in the percentage being treated for hypothyroidism as measured as percentage of women in both England which is lower and growing faster (6.1% to 6.7%) and Wales which is higher but growing more slowly (7.2% to 7.6%) (Figure 2A). The growth in prescribing of levothyroxine has been steady in both nations over the period examined, although at different rates. The total costs of hypothyroidism treatment per patient are similar in both countries and overall have risen in the last 8 years due to the cost of liothyronine with some reduction more recently since early 2017 (Figure 2A).

In England, there was a decline in numbers prescribed liothyronine following the 450% price increase 2013–2016. The price increase for liothyronine has now reversed by 30% from £3202 to £2390 per annualized DDD per year but it remains 4 times 2012 levels (Figure 2B). Use of liothyronine in the hypothyroidism cohort has only dropped from 0.92% to 0.53% with 57% continuing to use this therapy in spite of the price increase. In Wales, the numbers on liothyronine grew before 2014 at 6% per year up to 386 individuals. The price increased by a factor of 550% from £642/year to £3521/year. Since 2014–15, the number on liothyronine has been declining by 5% per year to 310 currently. The price of liothyronine has now decreased by 23% to £2728/year. And overall use has declined from 0.51% to 0.4% so 75% continuing to use this therapy in spite of the price increase.

In England (Figure 2B), 0.92% of individuals on thyroid hormone replacement were on liothyronine in 2011–12 and that has fallen by 40% to 0.53% by 2019–20. In Wales, a smaller percentage (0.46%) were on liothyronine therapy at the start of the period but prescribing volume fell by only 15% to 0.40% at the end of the period. The costs of liothyronine were the same in both nations in 2011–12 but have diverged, with costs in Wales now being 10% higher than England (£2722 Wales vs. £2386/year England).

There was 20% more treatment for hypothyroidism in Wales than in England and growth in annual amount prescribed was 5% in

Wales compared to 10% in England. The average spend per person was similar.

3.5 | Variation in prescribing by CCG in England in 2019/20

In England, there are 135 local clinical commissioning groups of different sizes. There was significant variation across CCGs in liothyronine prescribing with much less variation in prescribing of levothyroxine (Figure 3). All clinical commissioning groups (CCGs) had at least one liothyronine prescribing practice, with 51.5% of general practices not prescribing any liothyronine.

There was some variation in the identification and treatment of hypothyroidism (with levothyroxine) across different CCGs, and the median is 7% of the population of women age > 30. The lowest decile region is 5.5% and the highest decile is 8.3% of women >30 years old. Variation in use of liothyronine is higher. The median is 0.4% of those being treated with Levothyroxine. The lowest decile is 0.1% and highest decile 0.9% of those treated with levothyroxine.

4 | DISCUSSION

This data highlight the ongoing rise in levothyroxine prescribing in England and Wales. The total number of individuals on Levothyroxine increased by a rate of 3% and 1.5% per annum in England and Wales, respectively. This is likely multifactorial, reflecting an ageing population and widespread use of thyroid function tests. Previous studies have shown a steady fall in TSH threshold at initiation of levothyroxine,¹⁵ but it is unclear whether this has continued. In contrast, there was a relative decline in liothyronine prescribing following a peak from about 2015–2017.

No new major trials of liothyronine have been performed in recent years, indicating that the changes we have observed are economically driven rather than clinically driven. Guidance has generally been equivocal or has actively discouraged liothyronine prescribing.^{4–6,9} There was a greater decrease in liothyronine prescribing in England than in Wales where the price has remained lower, albeit net increased since 2011.

In spite of strenuous attempts to limit prescribing of liothyronine in general practice, our findings show that a significant number of doctors continue to prescribe liothyronine. In England, priorities for primary care are set by the local clinical commissioning groups of which there are 135 of different sizes. Notably, all CCGs had at least one liothyronine prescribing practice suggesting a continued need for this treatment whether driven by patients or their clinicians. This is in the context of various sets of guidance published in the last decade^{4–6,9} which have largely left open the possibility of liothyronine being legitimately prescribed. The pattern of prescribing of liothyronine in Wales would also support this.

We have seen a steady increase in levothyroxine prescribing over the last 8 years which may relate to the increased number of

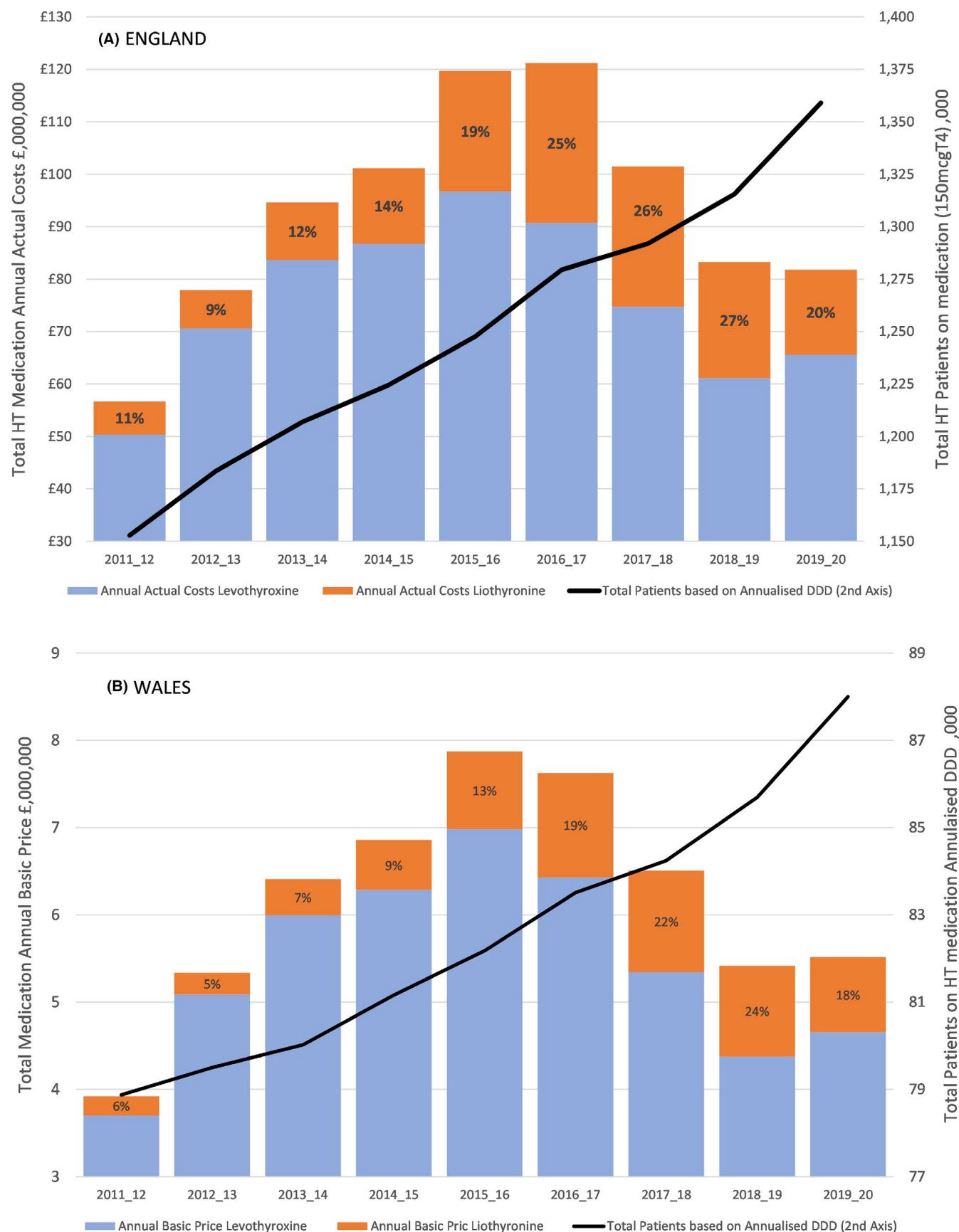
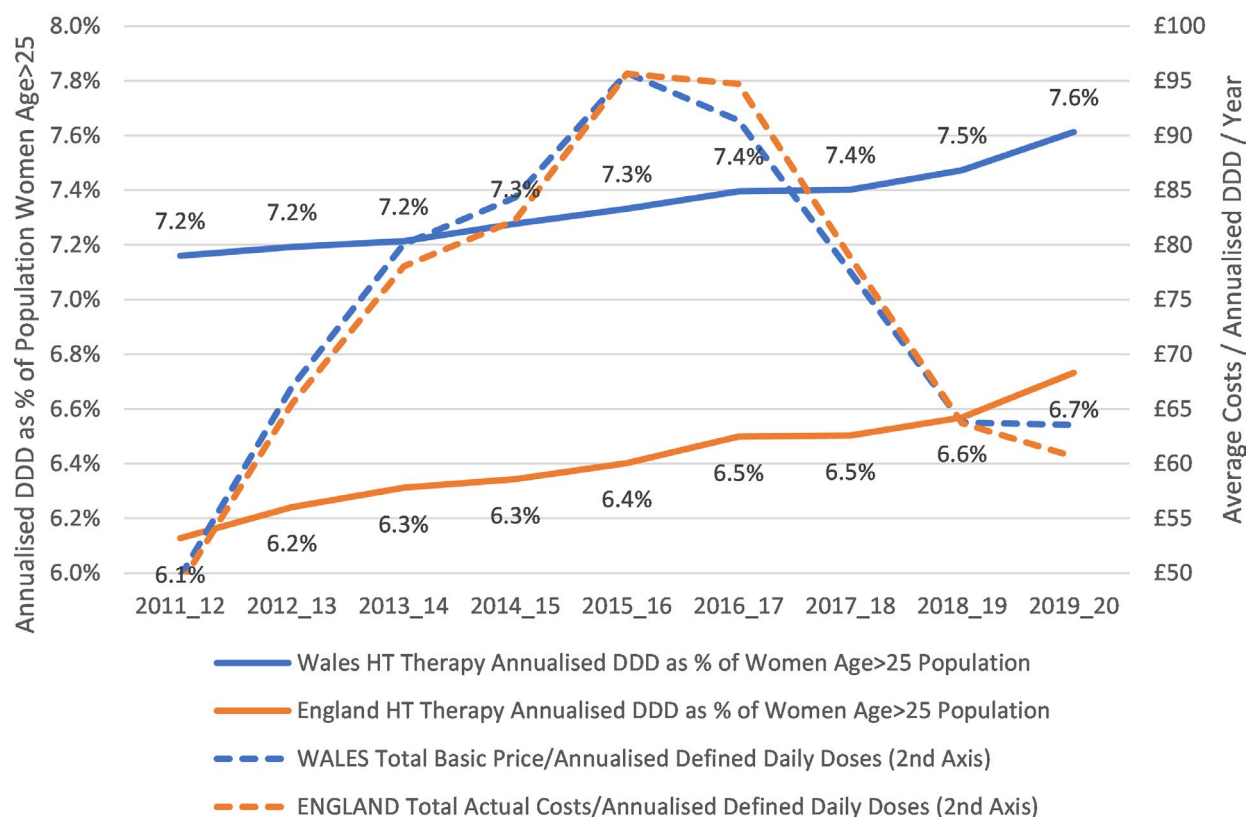


FIGURE 1 Annual trends in thyroid hormone replacement prescribing 2011-12 to 2019-20 for (A) England and (B) Wales. The bars represent the relative total costs of levothyroxine and liothyronine. The black line describes the volume of prescribing of levothyroxine as converted to total annualized patients at 150 mcg/day. The orange colour represents annual cost of liothyronine and the blue colour the annual cost of levothyroxine [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

(A) Hypothyroidism (HT) Therapy (T3, T4, NDT) in Wales & England



(B) Liothyronine & NDT Treatment in Wales & England

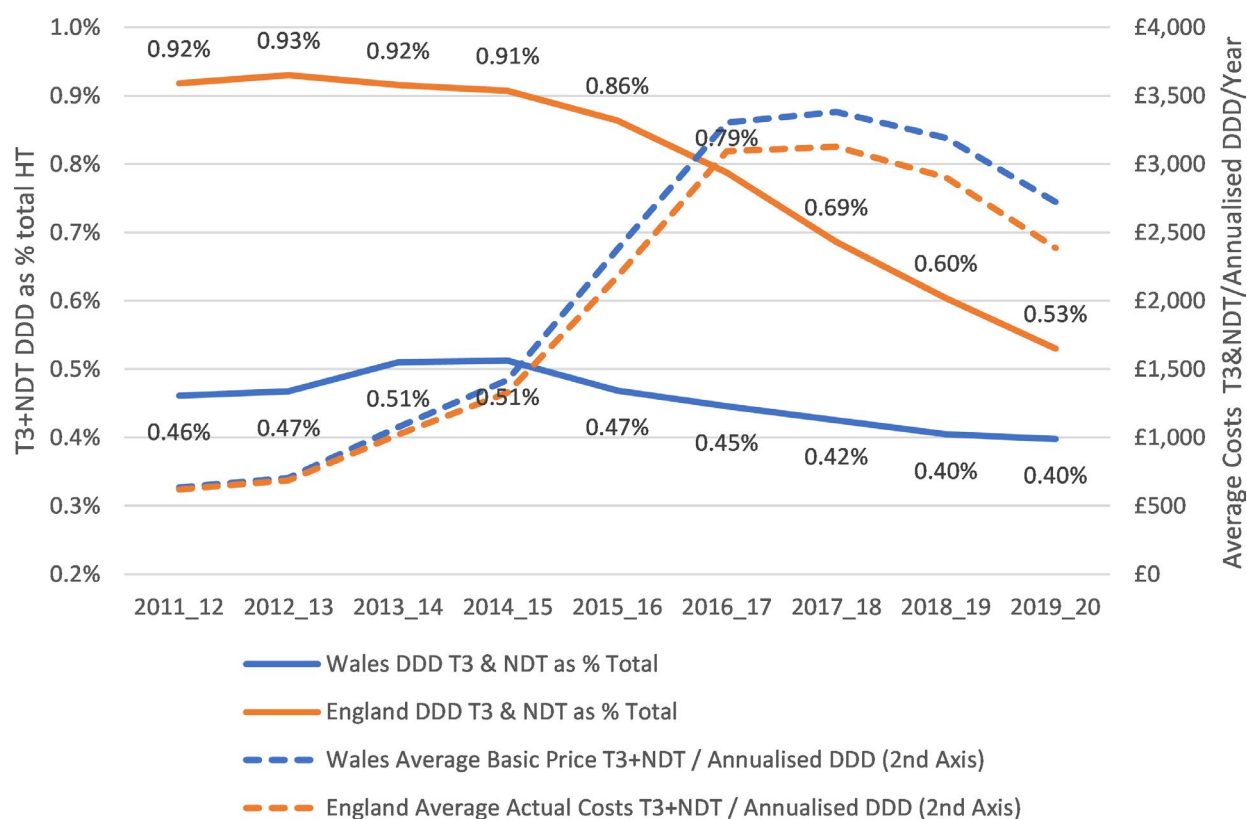


FIGURE 2 Relative growth in number of individuals treated and cost of treatment for (A) hypothyroidism in England and Wales and (B) Use of Liothyronine and NDT over the period 2011–12 to 2019–20 [Colour figure can be viewed at wileyonlinelibrary.com]

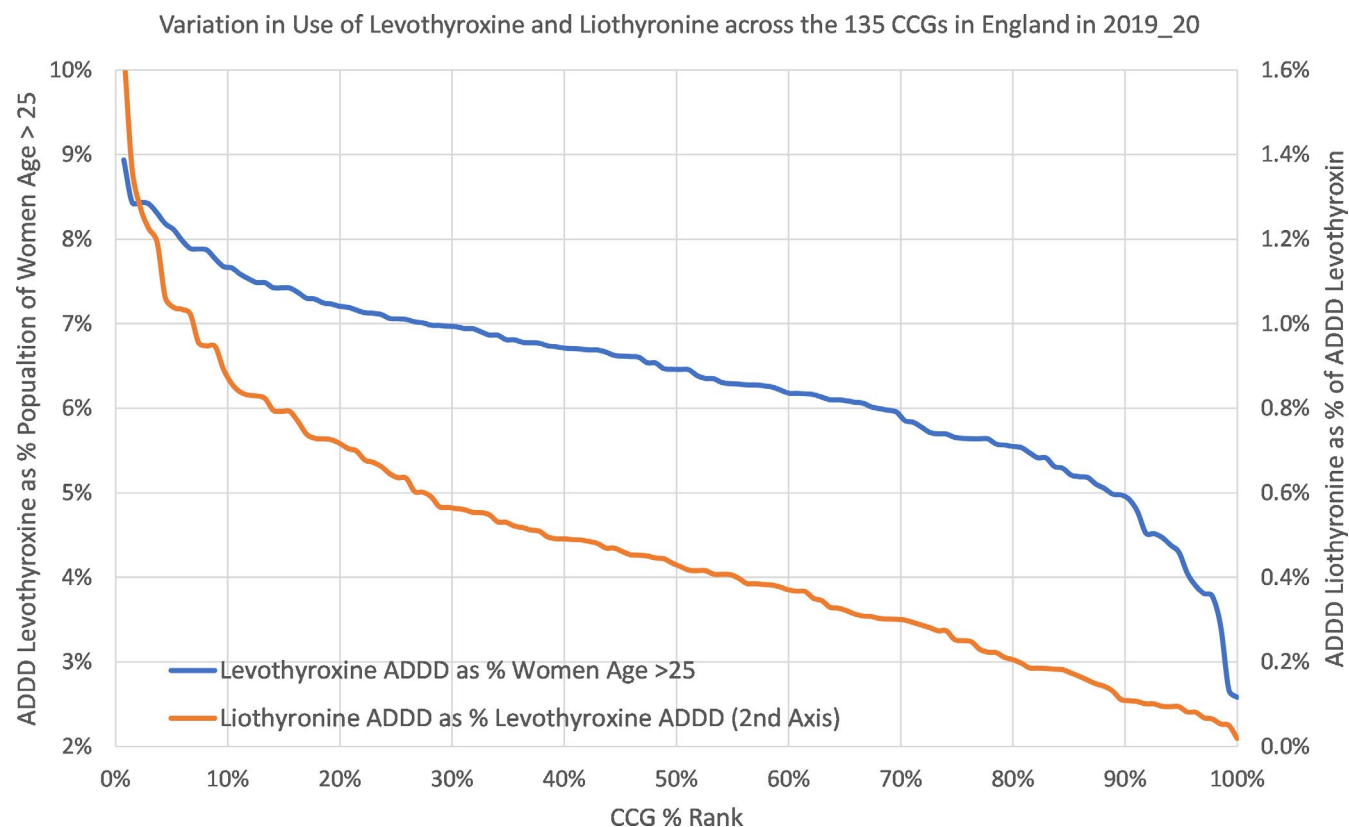


FIGURE 3 Percentage of levothyroxine and liothyronine prescribing across for all CCGs in England (Ranked by Deciles) [Colour figure can be viewed at wileyonlinelibrary.com]

older people in the population of England and Wales in that period,¹⁴ while also being a consequence of prescription of levothyroxine in people with borderline hypothyroidism.¹⁵ We found a difference between England and Wales with much less of a decrease in liothyronine prescriptions in Wales over recent years. Given the significantly smaller size of the population served by the National Health Service (NHS) in Wales, a factor in Wales may be the influence of local opinion leaders who support prescription of liothyronine in combination with levothyroxine where appropriate.

It is possible that the reduction in prescribing of liothyronine, captured in the data here, may be missing patients discontinuing NHS prescriptions but choosing to obtain ongoing private prescriptions or non-prescription sources of liothyronine and of NDT; this cannot be captured in this sort of analysis.

NHS data reflecting a reduction in non-conventional prescribing may therefore be missing a cohort of patients seeking private liothyronine and NDT who may not be being monitored for safety or harm. Whilst this hidden group may not be possible to quantify, it should be noted that they are likely to exist and current prescribing pattern changes may lead to an increase in this disenfranchised group of patients who may be inadequately treated and monitored and who may come to harm from this change in NHS prescribing patterns.

4.1 | Cost

Levothyroxine is on the World Health Organization's List of Essential Medicines, that is, the safest and most effective medicines needed in a health system. The wholesale cost in the developing world is about £0.43 (US\$0.58) (bb) to £9.20 (US\$12.28) per month.¹⁵ In the United States, a typical month of treatment costs less than US\$25 (£18.72). Levothyroxine was the third most commonly prescribed medication in the United States in 2017, with more than 101 million prescriptions issued per year.

Liothyronine is available as a generic medication. A month's supply in the United Kingdom costs the NHS about GB £247 (US\$330) as of 2019. In the United States, the wholesale cost of this amount is about US\$22.40 (£16.80). In 2017, liothyronine was the 252nd most commonly prescribed medication in the United States, with more than one million prescriptions per year.¹⁶

Taylor et al¹⁷ similarly looked at prescribing of liothyronine over time in England and noted that the change in prescribing was largely driven by cost. They showed that between August, 2013, and July, 2018, there was a median 37% reduction in the ratio of liothyronine prescriptions per 1000 levothyroxine prescriptions nationwide, with a maximum 32-times reduction in one CCG. Analysis of CCG demographics in that study showed that for that for each quintile increase in economic deprivation, liothyronine prescriptions were 0.21 standard deviations lower.

Judgements on the cost-effectiveness of liothyronine in the UK appear to be made implicitly in policy guidelines, driven in large part by the significant difference in the current unit acquisition cost between liothyronine and levothyroxine. Guidelines either consider liothyronine/levothyroxine combination therapy to be non-inferior to levothyroxine alone (based on the available weak clinical evidence), or to be inferior because of the shorter pharmacokinetic elimination half-life and safety concerns. Neither perspective is fully justifiable, as the current evidence base is not targeted to the specific population in question, and inferiority has not been demonstrated. Pending further studies to clarify the role of combination therapy, patients who derive symptomatic benefit from it should not be deprived of treatment for economic reasons alone.

It has been stated that 5%–10% of people with hypothyroidism may be unresponsive to levothyroxine.² However, only a small proportion of these are currently receiving liothyronine. At present, it remains to be seen what proportion of these will benefit from liothyronine either in its current form or in the form of newer longer acting preparations currently under development. Certainly, recent evidence has shown that a small but significant proportion of people treated for hypothyroidism remain actively symptomatic.^{18,19} Interestingly, it is noteworthy that even in the 1970s it was recognized that some patients did not feel well on levothyroxine monotherapy and seemed to prefer liothyronine being used in combination with levothyroxine.²⁰

Decisions concerning the formulary restriction, deprescribing or disinvestment in liothyronine prescribing ought to consider the potential implications, which are both clinical and economic, and specific to individual patients. Perhaps, now is the time for the NHS to consider negotiating with the liothyronine suppliers given the very low cost of this drug in other countries (eg, in Australia the cost for 100 tablets of 20 microgram strength is only AUD\$69 or £38 pound.²¹

4.2 | Quality of life implications

Most guidance documents advocate a 3-month trial period, as modelled in the current analysis, when initiating liothyronine in eligible populations. Deprescribing may be appropriate on a case-by-case basis, and with patient agreement.¹⁹ However, there is no published analysis on quality of life and other health-related outcomes when liothyronine is stopped. Finally, some general practitioners prescribing liothyronine may be doing so after an endocrinologist has assessed the patient and recommended the use of liothyronine with levothyroxine in keeping with the British, European and US guidelines.^{4–6}

4.3 | Strengths/Limitations

While we have not looked at data from Scotland and Northern Ireland, there is no reason to suspect that the findings here would not be applicable to the other parts of the UK, albeit that the NHS

is organized differently in each of the other two nations. Also we have not here looked specifically at the prescribing of NDT at general practice level nor in trends of prescribing over time. This will be the subject of a further paper. Finally, we were not able to look specifically at prescribing of liothyronine alone.

5 | CONCLUSION

Levothyroxine prescribing has increased but in spite of strenuous attempts to limit prescribing of liothyronine in general practice, a significant number of doctors/patients still feel that this treatment is beneficial in Wales and in England. Given how common hypothyroidism is, adequately powered clinical trials of liothyronine/levothyroxine replacement are still urgently needed.

The price differential of liothyronine vs levothyroxine should be examined again, given that a proportion of both clinicians and patients perceive benefit in combination treatment.

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AUTHOR CONTRIBUTION

MS and AH conceived of the project, MS carried out the analysis, MS and AH prepared the report with PT, LP, OO and CD contributing to the introduction, interpretation and discussion.

CONFLICT OF INTEREST

None of the co-authors has any conflict of interest.

DATA AVAILABILITY STATEMENT

All the data used in the analyses presented are publically available and can be also made available from MS, co-author on application.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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